PAMELA GEHRON ROBEY
CSDB/NIDR/NIH Bldng 30 Rm 228
30 CONVENT DRIVE MSC 4320
BETHESDA, MD 20892

ATTN:
PHONE: 301-496-4563
FAX: 301-402-0824
E-MAIL:

NIH Fiche to Paper Journal

TITLE:	MEDICINE; ANALYTICAL REVIEWS OF GENERAL MEDICINE, NEUROLOGY, PSYCHIATRY, DERMATOLOGY, AND PEDIATRIES
PUBLISHER/PLACE:	Lippincott Williams _Wilkins Hagerstown, Md :
VOLUME/ISSUE/PAGES:	1996 Jul;75(4):171-84 171-84
DATE:	1996
AUTHOR OF ARTICLE:	Ringel MD; Schwindinger WF; Levine MA;
TITLE OF ARTICLE:	Clinical implications of genetic defects in G prot
ISSN:	0025-7974
OTHER NOS/LETTERS:	Library reports holding volume or year 2985248R 8699958
SOURCE:	PubMed
CALL NUMBER:	W1 ME648
REQUESTER INFO:	AB424
DELIVERY:	E-mail: probey@DIR.NIDCR.NIH.GOV
REPLY:	Mail:

0025-7974/96/7504–0171$03.00/0
MEDICINE

Vol. 75, No. 4
Printed in U.S.A.

Reviews in Molecular Medicine

Clinical Implications of Genetic Defects in G Proteins

The Molecular Basis of McCune-Albright Syndrome and Albright Hereditary Osteodystrophy

MATTHEW D. RINGEL, M.D., WILLIAM F. SCHWINDINGER, M.D., PH.D., AND MICHAEL A. LEVINE, M.D.

Introduction

Heterotrimeric signal transducing guanine nucleotide binding proteins (G proteins) couple extracellular receptor proteins to intracellular effector enzymes and ion channels, serving as critical mediators of cellular responses to external stimuli. These proteins are a subset of a larger family of guanosine triphosphate (GTP)-binding proteins of differing molecular weight and subunit composition that share a common mechanism of GTP-binding and hydrolysis that regulates protein activity. G proteins are comprised of 3 subunits (α, β, and γ) each encoded by many different genes. The multiplicity of G protein subunits facilitates great combinatorial variability, which, in part, accounts for the ability of G proteins to interact with many different receptor and effector proteins. Over 100 G protein-coupled receptors have been identified. The receptors share a common serpentine structure consisting of 7 membrane-spanning domains, and detect extracellular signals as diverse as light, odorants, hormones, growth factors, and neurotransmitters (12). G proteins regulate many second messenger systems, including enzymes such as adenylyl cyclase (AC), phospholipase C (PLC), and phospholipase A_2, as well as ion channels.

There are 2 classes of mutations in G proteins. *Activating mutations* in the gene (*GNAS1*) encoding the α subunit of the G protein that stimulates AC ($G\alpha_s$) have been identified in patients with McCune-Albright syndrome (MAS), a disorder characterized by increased hormone secretion and cellular proliferation of many endocrine tissues (141, 166). By con-

From the Division of Endocrinology and Metabolism, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Supported in part by United States Public Health Service Grant RO1DK34281 (to MAL), a Clinical Associate Physician Award 3MO1RR00722-22S1 (to WFS) from the National Institutes of Health through the Johns Hopkins Outpatient General Clinical Research Center, and a Postdoctoral Fellowship Award from Pfizer, Inc. (to MDR).

Abbreviations used in this paper: AC, adenylyl cyclase; ADP, adenosine diphosphate; AHO, Albright hereditary osteodystrophy; cAMP, adenosine 3′,5′-cyclic monophosphate; DAG, diacylglycerol; FSH, follicle-stimulating hormone; GDP, guanosine diphosphate; GH, growth hormone; GHRH, growth hormone releasing hormone; GTP, guanosine triphosphate; IP_3, inositol 1,4,5 triphosphate; LH, luteinizing hormone; MAS, McCune-Albright syndrome; PFD, polyostotic fibrous dysplasia; PHP, pseudohypoparathyroidism; PIP_2, phosphatidylinositol 4,5-diphosphate; PKA, protein kinase A; PLC, phospholipase C; PTH, parathyroid hormone; PTHrP, PTH-related protein; TRH, thyrotropin-releasing hormone; TSH, thyrotropin (thryoid-stimulating hormone).

Address reprint requests to: Michael A. Levine, M.D., The Johns Hopkins University School of Medicine, Ross Building, Room 1029, 720 Rulland Street, Baltimore, MD 21205.

trast, *inactivating mutations* of the *GNAS1* gene are present in patients with Albright hereditary osteodystrophy (pseudohypoparathyroidism and pseudopseudohypoparathyroidism), a syndrome associated with resistance to multiple hormones that activate $G\alpha_s$-coupled receptors (91, 92, 122, 165). Experimental analysis of these 2 syndromes, which represent contrasting gain of function and loss of function mutations in the same gene, has extended our understanding of the clinical and biochemical consequences of dysfunctional G protein action and has provided a "bench to bedside" demonstration of the critical role that G proteins play in transmembrane signal transduction in humans. In this review, we focus on these 2 syndromes as a paradigm for understanding the clinical implications of altered G protein function.

G Protein Structure and Function

G proteins share a common heterotrimeric structure consisting of an α subunit and a tightly coupled βγ dimer. The α subunit interacts with the G protein receptor and the βγ subunits, binds GTP, and possesses intrinsic GTPase activity (16). At least 16 genes encode mammalian α chains; additional protein diversity results from the generation of alternatively spliced mRNAs. The distribution of some α subunits is highly tissue specific (for example, G_{olf} is restricted to olfactory neuroepithelium), while other α chains have a ubiquitous representation (for example, G_s is expressed in all tissues). The GTP-bound α chain is able to regulate the activity of membrane-bound effector molecules that generate intracellular "second messengers." The α subunits associate with a smaller group of β (5) and γ (10) subunits (51, 96, 133, 162). The β and γ subunits combine preferentially with one another (138, 139) and the resultant βγ dimers demonstrate preferred associations with specific α subunits (133, 134, 162). Thus, combinatorial specificity in the associations between G protein subunits generates enormous diversity and permits exquisite specificity in the interactions of G protein heterotrimers with receptors (79). At present it is unknown whether specific G protein subunit associations occur randomly or if there are regulated mechanisms that determine the subunit composition of heterotrimers.

G protein activity is regulated by the binding and hydrolysis of GTP by the α subunit (Figure 1). In the basal (nonstimulated) state, G proteins exist in the heterotrimeric form with guanosine diphosphate (GDP) tightly bound to the α chain. Upon receptor activation, a conformational change occurs in the α chain that facilitates the exchange of bound GDP for GTP, with subsequent dissociation of the α-GTP chain from the βγ dimer and the receptor. The free α-GTP chain is now able to interact with effector enzymes and ion channels to regulate their activity. In addition, free βγ dimers modulate the activity of at least some effectors (for example, certain forms of AC and PLC) and participate in receptor desensitization (30, 78, 125, 126). The interaction of α-GTP with the effector molecule is terminated by the hydrolysis of GTP to GDP by an endogenous GTPase. With hydrolysis of GTP to GDP, the α-GDP chain reassociates with the βγ dimer and the heterotrimeric G protein is ready for another cycle of receptor activation.

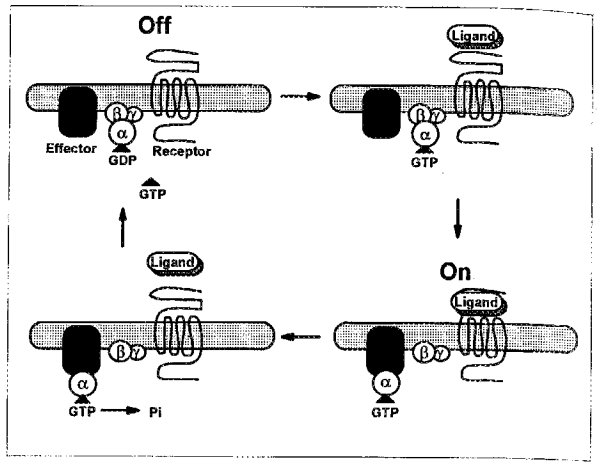

FIG. 1. The G protein GTPase regulatory cycle. In the nonstimulated ("off") state, the guanosine diphosphate (GDP) is bound to the α subunit. The α subunit is associated with the βγ dimer forming a heterotrimer (upper left). A ligand binds to a G protein-coupled receptor causing a conformational change in the receptor and G protein. The α subunit then exchanges GDP for guanosine triphosphate (GTP) (upper right). After binding GTP, the α subunit is activated (turned "on") and dissociates from the βγ dimer and the receptor. The GTP-bound α subunit regulates multiple effector molecules (lower right). GTP is hydrolyzed to GDP by the intrinsic GTPase activity of the α subunit (lower left). The inactive GDP-bound α subunit reassociates with the βγ dimer and the heterotrimeric G protein is ready for another cycle of activation.

X-ray crystallography and in vitro mutagenesis experiments have identified specific sequences in the α chain that determine the functional and physical interactions of the α chain with receptors, effectors, and βγ dimers. Moreover these studies have also defined regions that regulate binding and hydrolysis of GTP (11, 32, 57, 72, 84, 104, 115, 118).

Posttranslational modification of G protein subunits is required for both proper membrane localization and effective interactions with effector molecules. Coincident with G protein activation, all α subunits (except $G\alpha_t$) undergo lipid modification (palmitoylation) at a Cys residue near the NH_2-terminus. In addition, many α subunits (for example, $G\alpha_o$

and $G\alpha_i$) are myristolated at an NH_2 terminal glycine, a modification that increases affinity for $\beta\gamma$ dimers. The γ subunits are modified at the C-terminus by attachment of a farnesyl or geranygeranyl group to a Cys residue (163). These posttranslational modifications of the α and γ subunits are necessary for efficient G protein localization, coupling, and turnover.

G Protein-Coupled Signaling Cascades

G proteins that are coupled to serpentine receptors regulate activity of membrane-bound forms of AC and PLC. There are multiple isoforms of both AC (65, 116, 154) and PLC (135) which can be distinguished by their tissue distribution and ability to interact with α and $\beta\gamma$ subunits. Activation of AC leads to synthesis of adenosine 3′,5′-cyclic monophosphate (cAMP), the "second messenger" that activates protein kinase A (PKA). By contrast, stimulation of PLC leads to hydrolysis of phosphatidylinositol 4,5-diphosphate (PIP_2) with the subsequent production of diacylglycerol (DAG) and inositol 1,4,5 triphosphate (IP_3). DAG activates protein kinase C (PKC) while IP_3 releases calcium from intracellular stores. Both PKA and PKC initiate protein phosphorylation cascades that result in diverse cellular and genomic effects.

Activity of AC is under dual regulatory control by G proteins. Activation of receptors coupled to G_s (for example, the β adrenergic receptor) leads to stimulation of AC and increased synthesis of cAMP (21, 22, 149). In addition, many cells express other receptors that are coupled to G_i (for example, muscarinic receptors) which when activated lead to inhibition of AC (53, 54, 75). Moreover, $\beta\gamma$ dimers released by activation of G_s or G_i can also influence the activity of some forms of AC (30, 139, 153). Additional complexity derives from the observation that activity of several forms of AC are regulated by PKC, which is activated via the G_q-coupled PLC signaling pathway. Thus, AC acts as a coincidence detector, and its activity is determined by a complex and coordinate interplay between multiple G protein subunits and other regulators (for example, calcium-calmodulin).

In many endocrine tissues, synthesis of cAMP leads to increased hormone formation and cell growth via PKA-linked pathways. For example, in thyrocytes, thyrotropin (thyroid-stimulating hormone–TSH)-dependent stimulation of AC leads to activation of PKA, and the subsequent phosphorylation events lead to genomic (and nongenomic) effects that increase expression of the thyroglobulin gene and other genes important for thyroid hormone synthesis and thyrocyte growth (8, 108). These molecular events ultimately result in increased release of thyroid hormone and cellular proliferation (87, 160).

Similar to many other serpentine hormone receptors (for example, PTH, luteinizing hormone [LH], vasoactive intestinal peptide, calcitonin, glucagon-like peptide), the TSH receptor also stimulates the PKC phosphorylation cascade via G_q/G_{11}-dependent activation of PLC (8, 29, 40, 58, 160) (Figure 2). Binding of TSH to its receptor leads to activation of G_q and G_{11} which stimulate PLC. PLC subsequently hydrolyzes PIP_2 to DAG and IP_3 which activates PKC and increases intracellular calcium, respectively. Activation of this signaling cascade leads to thyroid cell growth but not hormone production.

As depicted in Figure 2, activation of the TSH receptor leads to the subsequent simultaneous activation of both the AC and PLC pathways, a process that facilitates crosstalk between these pathways. The $\beta\gamma$ dimers released from G_s and/or $G_{q/11}$ can modulate activity of certain forms of AC and PLC. Moreover, PKC can phosphorylate certain isoforms of G_i and AC, further influencing activity of these proteins. Additionally, the released $\beta\gamma$ dimers activate $p21^{ras}$, a key G protein regulating the mitogen-activated protein kinase pathway (34, 39). Thus, crosstalk between signaling pathways refines the hormonal control of cellular processes as diverse as cell growth and proliferation, metabolism, and gene transcription.

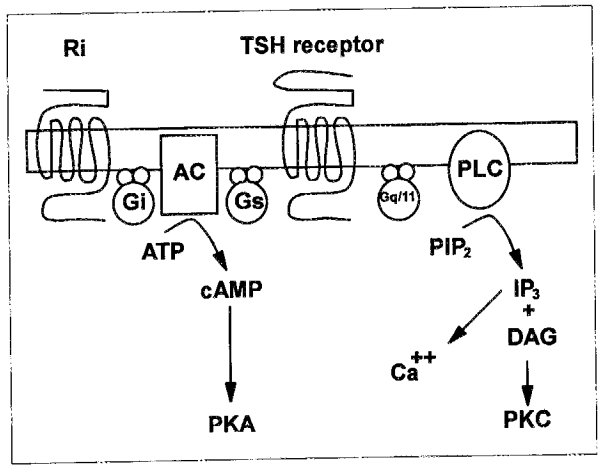

FIG. 2. Signal transduction pathways coupled to the thyrotropin (thyroid-stimulating hormone–TSH) receptor. The TSH receptor couples to the G proteins G_s and $G_{q/11}$ to activate adenylyl cyclase (AC) and phospholipase C (PLC), respectively. R_i, a generic receptor for ligands that inhibit adenylyl cyclase, is depicted as coupling to G_i. The subunit structure ($\alpha\beta\gamma$) of the G proteins and their interactions with effector proteins are described in the text. Abbreviations: PKA = protein kinase A; PKC = protein kinase C; DAG = diacylglycerol.

$G\alpha_s$ Gene Defects

The human $G\alpha_s$ subunit is encoded by the *GNAS1* gene located on chromosome 20q13.1–13.2 (95). It contains at least 13 coding exons (81) and can be alternatively spliced to yield 4 different protein isoforms with similar biological activities (17). In addition, there are at least 2 alternative first exons that produce transcripts encoding 1) a truncated, nonfunctional $G\alpha_s$ protein that uses an initiator ATG sequence in exon 2 (69), and 2) a larger (92 kDa) protein, termed $XL\alpha_s$, of uncertain function that is produced by the fusion of a novel 51 kDa protein to the protein encoded by exons 2 through 13 of $G\alpha_s$ (76).

Somatic and germline mutations in *GNAS1* that lead to either gain of function or loss of function have been identified in patients with disorders characterized by hormone-independent cellular proliferation or hormone resistance, respectively.

Activating Mutations of $G\alpha_s$ in Oncogenesis

Vallar et al (158) initially described a subset of human growth hormone-secreting pituitary tumors that exhibited increased adenylyl cyclase activity in the absence of growth hormone releasing hormone (GHRH). Landis et al (86) subsequently identified the molecular basis for constitutive activation of AC as somatic mutations in *GNAS1* that resulted in the replacement of either Arg^{201} or Gln^{227}. These 2 *GNAS1* missense mutations, which convert the *GNAS1* gene to an oncogene termed *gsp*, enable the $G\alpha_s$ subunit to remain in the active, GTP-bound state. Such activating mutations occur in 8%-43% of growth hormone-secreting tumors.

Arg^{201} is the site for ADP-ribosylation by *Vibrio cholera* exotoxin. This covalent modification inhibits the intrinsic GTPase of $G\alpha_s$ and results in ligand-independent stimulation of adenylyl cyclase (73). The subsequent accumulation of cAMP in intestinal epithelial cells is responsible in part for the secretory diarrhea associated with cholera.

Gln^{227} corresponds to the cognate amino acid, Gln^{61}, that is frequently replaced in the low molecular weight GTP-binding protein ras to convert it to an oncogene. Mutations in $p21^{ras}$ that replace Gln^{61} are present in a variety of human tumors (39, 55). These mutations inhibit the GTPase activity of the $p21^{ras}$ protein and lead to constitutive activation of signaling pathways that are transforming in vitro (97, 131, 148). Arg^{201} and Gln^{227} are located in the G3 and G4 domains of $G\alpha_s$, which correspond to domains that are required for GDP/GTP binding and intrinsic GTPase activation, respectively (10, 64, 119).

In addition to growth hormone-secreting pituitary tumors, $G\alpha_s$ mutations are present in a subset of functioning and nonfunctioning benign and malignant thyroid neoplasms, but are rare in other endocrine tumors (Table 1).

McCune-Albright Syndrome

Molecular basis of McCune-Albright syndrome

In 1937, McCune and Bruch (107) and Albright and associates (6) independently described a sporadic syndrome characterized by the clinical triad of polyostotic fibrous dysplasia, café au lait skin lesions, and endocrine hyperfunction now known as McCune-Albright syndrome (MAS).

Evidence suggesting that the basis for MAS involved constitutive (that is, hormone-independent) activation of the AC signaling pathway in affected tissues included the following: 1) cAMP is the critical second messenger leading to cellular proliferation and/or function in affected tissues, and 2) despite excessive activity of endocrine tissues, serum levels of the relevant regulatory or tropic hormones were either normal or decreased, suggesting autonomous function. Because each affected cell type expresses different receptors, a postreceptor defect in a protein that is present in all affected tissues was proposed as a unifying molecular etiology for MAS. The identification of activating mutations of $G\alpha_s$ in growth hormone-secreting pituitary tumors and autonomously functioning thyroid tumors made *GNAS1* an attractive candidate gene.

Mutations in *GNAS1* causing the replacement of Arg^{201} [Arg^{201}(CGT)→His(CAT) and Arg^{201}(CGT)→Cys(TGT)] have been described independently by Weinstein et al (166) and Schwindinger et al (141) in DNA isolated from tissues obtained from patients

TABLE 1. Clinical syndromes associated with activating mutations of GNAS1*

McCune-Albright syndrome (100%)
Pituitary adenomas (8%-43%)
Growth hormone-secreting adenomas (14, 31, 85, 86, 100, 150, 158)
ACTH-secreting adenomas (14, 168)
Clinically nonfunctioning adenomas (14, 100, 155, 167, 172)
Thyroid neoplasms (3%-70%) (55, 56, 105, 109, 117, 151)
Hyperfunctioning and nonfunctioning follicular adenomas
Papillary and follicular carcinomas
Parathyroid neoplasms (<5%)
Parathyroid ademonas (14, 161, 169)
Adrenocortical disorders (<5%)
Aldosterone-producing ademonas (172)
Adrenal hyperplasia (169)
Pheochromocytoma (169)

* Missense mutations of *GNAS1* and Arg^{201} and Gln^{227} that cause constitutive activation of adenylyl clyclase and the cAMP signaling cascade have been identified in patients with McCune-Albright syndrome and subsets of a variety of endocrine tumors.

with MAS. Cells containing these mutations are present in affected endocrine tissues, skin, and bone from patients with MAS. *GNAS1* activating mutations are not present in all cells of affected patients, however, even within affected organs. Mutation-bearing cells are distributed in a mosaic pattern, with the greatest number present in the most abnormal areas of affected tissues (141, 146). Moreover, the gene mutation is also present in cells not typically affected by MAS, including blood, liver, and heart (141, 145, 146).

These molecular studies have confirmed the hypothesis first suggested by clinical observations of variable involvement of endocrine organs and skeleton and a distribution of skin lesions coinciding with lines of embryologic development: that the genetic mutation in MAS is not germline but rather is a postzygotic somatic mutation (60). The lack of documented heritability of MAS suggests that germline transmission of the mutation would be lethal.

Clinical manifestations of McCune-Albright syndrome

We reviewed the English literature by MEDLINE (National Library of Medicine, Bethesda, MD) search (1966–1995) and cross-referencing (1926–1995) and identified 158 reported cases of MAS. The clinical data are summarized in Table 2 and are discussed in detail below. It is difficult to determine the precise prevalence of clinical and endocrine manifestations of MAS from these studies owing to technical differences in diagnostic sensitivity over time, and a probable bias toward reporting patients with more severe or atypical manifestations of the disorder.

Polyostotic fibrous dysplasia (PFD): Nearly all (98%) patients with MAS have solitary or multiple expansile fibrous dysplasia lesions. These lesions typically develop during the first decade of life (see Table 2), and can cause progressive deformity, fractures, and nerve entrapment. The femur and pelvis are most commonly involved. Radiographs of affected bones reveal expansile, lytic lesions with a "ground glass" pattern and a scalloped border secondary to endosteal erosion (62, 88). Bone histology discloses uniform, benign-appearing whorled bundles of fibrous tissue with embedded fiber-bone trabeculae. These lesions bear some resemblance to those found in hyperparathyroidism (osteitis fibrosa), but PTH levels are not elevated in MAS. Solitary lesions (mono-ostotic fibrous dysplasia) are present in a minority of patients with MAS.

Osteosarcomas occurred in some MAS patients (mean age, 36 yr) (44, 61, 62, 136). In most cases the patient died as a result of the osteosarcoma. Accordingly, patients with MAS should be monitored carefully for the development of osteosarcomas. These tumors are not associated with treatment of the fibrous dysplasia with external beam radiation therapy. It is not known whether these osteosarcomas represent malignant degeneration of fibrous dysplasia.

PFD also occurs in patients without MAS, and may be associated with the development of myxomas, sarcomas, and hyperparathyroidism (42, 44, 61, 62, 129, 136). To date, none of these lesions have been reported to contain a $G\alpha_s$ mutation.

Café au lait skin lesions: Patients with MAS typically have 1 or more pigmented macules, termed café au lait lesions, that have irregular borders ("coast of Maine"). By contrast, café au lait skin lesions that occur in patients with neurofibromatosis (Von Rec-

TABLE 2. Clinical manifestations of McCune-Albright syndrome in 158 reported cases*

Manifestation	Patients (n = 158)	Male (n = 53)	Female (n = 105)	Age at Diagnosis (yr) (Range)	Comments
Fibrous dysplasia	154	51	103	7.7 (0–52)	Polyostotic more common than monostotic
Café au lait lesions	135	49	86	7.7 (0–52)	Variable size and number of lesions, irregular border ("coast of Maine")
Precocious puberty	82	8	74	4.9 (0.3–9)	Common initial manifestation
Acromegaly/gigantism	42	20	22	14.8 (0.2–42)	17/26 with adenoma on MRI/CT
Hyperprolactinemia	23	9	14	16.0 (0.2–42)	23/42 of acromegalics with ↑ PRL
Hyperthyroidism	30	7	23	14.4 (0.5–37)	Euthyroid goiter is common
Hypercortisolism	9	4	5	4.4 (0.2–17)	All primary adrenal
Myxomas	8	3	5	34 (17–50)	Extremity myxomas
Osteosarcoma	3	1	2	36 (34–37)	At sites of fibrous dysplasia, not related to prior radiation therapy
Rickets/osteomalacia	4	1	3	27.3 (8–52)	Responsive to phosphorous plus calcitriol
Cardiac abnormalities	17	8	9	(0.1–66)	Arrhythmias and CHF reported
Hepatic abnormalities	16	6	10	1.9 (0.3–4)	Neonatal icterus is most common

Abbreviations: MRI = magnetic resonance imaging; CT = computed tomography; PRL = prolactin; CHF = congestive heart failure.
* References provided in the text. Evaluations include clinical and biochemical data; other rarely described manifestations include metabolic acidosis, nephrocalcinosis, mental retardation, thymic and splenic hyperplasia, and colonic polyps.

klinghausen syndrome) have a smooth border ("coast of California"). The distribution of skin lesions in MAS is also characteristic: Lesions rarely extend beyond the midline, and the majority tend to be on the same side of the body as the skeletal lesions. They occur most commonly on the buttocks and lumbosacral regions. Happle (60) noted that lesions follow the lines of Blashko, embryologic lines of ectodermal migration, producing an S-shaped pattern on the chest, a V-shaped pattern on the back, and a linear distribution on the extremities. This clinical observation led to the hypothesis that MAS represented a somatic defect with mosaicism (as described above).

Endocrine abnormalities: Endocrine disorders are common in MAS and are characterized by autonomous and excessive function of hormone-producing tissues (see Table 2). Serum concentrations of tropic or stimulating hormones are typically normal or reduced. The most common endocrine disorder is gonadal hyperfunction. Eighty-two of 133 (62%) patients reported in the literature who were evaluated for ovarian or testicular function were found to have abnormally elevated sex hormones with low or undetectable serum levels of gonadotropins (6, 13, 20, 28, 35–37, 43–46, 49, 50, 52, 61–63, 68, 77, 80, 88, 89, 98, 99, 102, 103, 106, 113, 127, 129, 130, 143, 144, 146, 156).

Precocious puberty is a common initial manifestation of MAS in girls, and is readily recognized by the development of secondary sexual characteristics prior to age 9 years. In general, estrogen levels are elevated as a result of excessive ovarian function, and serum levels of LH and follicle-stimulating hormone (FSH) are low (88). Sex hormone secretion is typically not associated with follicular maturation and ovulation. Patients show prepubertal LH responses to infusion of GnRH, a characteristic of gonadotropin-independent precocious puberty (that is, precocious "pseudopuberty") (49). Benign ovarian cysts may occur, and surgical excision may result in regression of secondary sexual characteristics until the onset of normal pubertal development. As adults, these women are generally fertile, although they may have occasional irregular menses due to continued gonadotropin-independent production of estrogen (13, 88). Treatment of girls with MAS and precocious puberty with testalactone, an aromatase inhibitor, has been successful for short periods of time, but long-term (1–3 yr) treatment has been disappointing (45, 63).

Pituitary-independent precocious puberty also occurs in boys with MAS, but it is much less common than in young girls. Approximately 10% (8/82) of reported MAS patients with precocious puberty are male. Testicular biopsy in these cases reveals variable degrees of seminiferous tube development and Leydig cell hyperplasia (101).

Growth hormone (GH) excess and/or hyperprolactinemia are common in patients with MAS (3, 4, 13, 19, 23, 28, 33, 35, 37, 44, 47, 52, 61, 66, 71, 80, 82, 83, 88, 89, 98, 99, 106, 111, 121, 127, 128, 130, 132, 144, 146, 147, 152). Many patients will also have features of acromegaly and galactorrhea. Gigantism in children and adolescents has also been well described. While the female:male ratio of MAS patients is approximately 2:1, increased growth hormone secretion occurs in approximately equal numbers of males and females (20 versus 22).

The biochemical behavior of growth hormone-producing pituitary tumors in patients with MAS is indistinguishable from that of sporadic tumors with and without *gsp* mutations. GH secretion is stimulated by thyrotropin-releasing hormone (TRH), GHRH, and sleep, and is incompletely suppressed by glucose administration (35). However, only 65% of MAS patients with growth hormone excess have radiographic evidence of a pituitary tumor, a much lower incidence than in sporadic cases of acromegaly (99%) (35). In addition, hyperprolactinemia occurs in over 50% (23/42) of MAS patients with elevated GH levels, a frequency somewhat greater than that occurring in patients with sporadic pituitary tumors (40%).

Pituitary pathology in patients with MAS includes adenoma, nodular hyperplasia, and mammosomatotrope hyperplasia. Surgery may be technically difficult if there is coexisting PFD of the base of the skull. Despite this potential complication, both open- and trans-sphenoidal hypophysectomies have been successfully performed. Adjuvant and primary therapy with external beam irradiation have also been reported (28, 66, 144, 147). Despite concerns regarding increased risk of developing osteosarcoma in regions of bone with PFD, no case of radiation-induced osteosarcomas has been reported in MAS.

Medical therapy with somatostatin analogs and bromocriptine has been shown to reduce tumor size and hormonal secretion in some, but not all, patients (23, 33, 47, 52, 80, 130, 147, 152).

Autonomous thyroid nodules and hyperthyroidism have been reported in 30 of 91 (33%) MAS patients who underwent thyroid evaluation (3, 4, 20, 36, 44–46, 48, 52, 62, 68, 82, 88, 111, 129, 132, 146, 173). Thyroid nodules have been treated by radioactive iodine ablation or surgery. The degree of hyperthyroidism is variable, and serum concentrations of TSH are typically low. The thyroid gland will often appear normal by physical exam, but nodules are nearly always detectable by sonography (48). Patients lack clinical or serologic evidence of autoimmune thyroid disease, and thyroid-stimulating immunoglobulins are undetectable.

Patients with MAS occasionally develop autonomous function of the adrenal gland and primary hypercortisolism (1, 9, 15, 37, 77, 106, 146, 173) at a young age (mean age, 4.4 yr). In contrast to pituitary-dependent Cushing disease, the elevated concentrations of cortisol are not suppressed by administration of high-dose dexamethasone, and serum levels of ACTH are low or undetectable. Adrenal gland histopathology reveals either nodular hyperplasia or solitary adenoma (106).

Hypophosphatemic rickets and osteomalacia can develop in patients with polyostotic fibrous dysplasia, with or without the MAS phenotype. Four patients with MAS have been diagnosed with osteomalacia or rickets (59, 77, 90). These patients have an abnormally low renal tubular maximum for the reabsorption of phosphorous per liter of glomerular filtrate (TmP/GFR), indicative of renal phosphate wasting and subsequent hypophosphatemia that leads to rickets or osteomalacia. The pathophysiologic basis for the hyperphosphaturia remains unknown. A similar clinical syndrome of hyperphosphaturia with subsequent osteomalacia or rickets occasionally associated with glucosuria and/or aminoaciduria has been described in X-linked hypophosphatemic rickets and in patients with various tumors of generally mesenchymal origin (oncogenic or tumor-associated osteomalacia). In patients with tumor-associated osteomalacia, renal transport of phosphate becomes normal after removal of the tumors, thus implicating tumor production of a humoral factor (41).

Two theories have been proposed to explain hyperphosphaturia in MAS: 1) the production of a circulating phosphaturic factor, termed phosphatonin (41), by fibrous dysplasia lesions; or 2) an intrinsic defect in renal tubular reabsorption of phosphate. Recent studies suggest that both hypotheses are plausible. Activating mutations of $G\alpha_s$ have been identified in the kidneys of patients with MAS, and could result in excess generation of cAMP in proximal tubular cells and consequent reduction in TmP/GFR. Indeed, basal levels of nephrogenous cAMP are elevated in MAS patients with hypophosphatemia despite normal serum levels of PTH (174). However, these observations cannot exclude the possibility that a circulating phosphaturic factor is also present in MAS patients with hypophosphatemia. The occurrence of hypophosphatemic osteomalacia in patients with isolated fibrous dysplasia supports the notion that similar bone lesions in patients with MAS may elaborate a phosphaturic factor.

Variability of tissue involvement: The tissue distribution of the *GNAS1* mutation in patients with MAS is not limited to endocrine cells. Activating $G\alpha_s$ mutations have been identified in peripheral blood leukocytes, liver, heart, thymus, and the gastrointestinal tract (141, 146). The presence of the *GNAS1* mutation in these tissues has in some patients been associated with clinical consequences such as hepatitis, cardiac arrhythmias, or intestinal polyps.

The variable clinical involvement of different tissues in patients with MAS likely reflects several biological effects. First, the *GNAS1* gene is mutated early in embryogenesis and therefore is distributed among a mosaic population of cells. The proportion and distribution of affected cells in a tissue will be determined by the precise stage in development in which the mutation occurred. Thus, mutational events that occur later in embryogenesis are likely to give rise to fewer mutant cells, and a milder phenotype, than mutational events that occur very early. A second determinant of clinical phenotype is based on the variable ability of cAMP to induce proliferation in different cells. Thus, mutational activation of $G\alpha_s$ will be most consequential in those tissues in which cAMP can stimulate cellular proliferation and/or hormone secretion. CAMP is not mitogenic in most cell types, and in some cell types cAMP can actually inhibit growth. For example, cAMP is not growth-promoting in fibroblasts, a model system commonly used to study growth regulation. Moreover, increased cAMP and activation of the PKA signaling cascade in NIH3T3 cells has been shown to reverse the transformed phenotype induced by activated $p21^{ras}$ (27, 39). Third, even in cells in which cAMP is a strong growth stimulator, counter-regulatory responses (such as increased cAMP phosphodiesterase activity [39, 114, 171]) may occur that can mitigate or even reverse the activated $G\alpha_s$ phenotype. Thus, a second genetic "hit" may be required for the development of autonomous nodules in some tissues, while in others, persistently elevated levels of cAMP may be sufficient to alter cellular phenotype. In fact, it is unknown whether the autonomous nodules in MAS patients represent the proliferation of mosaic rests of cells harboring the *gsp* mutation or if they result from the acquisition of additional gene mutations.

A more severe form of MAS characterized by jaundice, hepatitis, extramedullary hematopoiesis, gastrointestinal polyps, thymic hyperplasia, acute pancreatitis, neurodevelopmental disorders, and sudden cardiac death has been described (146). By extension, this unusually severe syndrome demonstrates the wide variety of cell types that are dependent on G_s-coupled receptors for normal function and are positively regulated by cAMP. The percentage of cells harboring the mutation may be greater than in the usual form of MAS, accounting for the more severe phenotype described in this group of patients.

Albright Hereditary Osteodystrophy, Pseudohypoparathyroidism, and Pseudopseudohypoparathyroidism

In 1942, Fuller Albright (5) described a group of patients with clinical and biochemical features of hypoparathyroidism (that is, hypocalcemia and hyperphosphatemia) who did not show a phosphaturic response to injected parathyroid extract. He suggested that hypoparathyroidism in these patients was not caused by a deficiency of parathyroid hormone (PTH) but was due to end organ resistance to PTH, and termed this condition "pseudo"-hypoparathyroidism (PHP). Thus, Albright was the first to recognize a human disease due to deficient responsiveness to a hormone by otherwise normal target organs. Albright also noted that these patients had a distinctive constellation of developmental and skeletal defects, including a round face, short stature, brachydactyly (shortened metacarpal and metatarsal bones), obesity, heterotopic ossifications, and mental retardation. Albright later identified other subjects who had many of these developmental defects but who lacked clinical evidence of hormone resistance; he termed this disorder "pseudo"- pseudohypoparathyroidism (pseudoPHP) to emphasize the physical similarities but biochemical differences between these patients and patients with PHP (7). This constellation of skeletal and developmental abnormalities, with or without hormone resistance, is now termed Albright hereditary osteodystrophy (AHO).

Molecular basis of PHP and AHO

The first clues to the molecular basis for hormone resistance in PHP came from the demonstration by Chase and Aurbach that the actions of PTH on its target organs, bone (25) and kidney (24), are mediated by cAMP. PTH infusion in normal subjects leads to increased urinary excretion of nephrogenous cAMP (26). By contrast to patients with idiopathic or postsurgical hypoparathyroidism, patients with PHP show a markedly blunted urinary cAMP response to exogenous PTH, whereas patients with pseudoPHP show a normal response (26). These observations have permitted the classification of PHP into type I and type II: In PHP type I, both the nephrogenous cAMP and phosphaturic response to PTH is blunted, whereas in PHP type II, a much less common variant of PTH resistance, there is a normal nephrogenous cAMP response to PTH infusion but a diminished phosphaturic response. These responses suggested that the defect in PHP type I was in the PTH receptor- adenylyl cyclase system, whereas the defect in PHP type II was likely to be in a more distal component of the cAMP signaling pathway. Subsequent clinical and biochemical studies have led to a further refinement in the classification of patients with PHP (Table 3).

Patients with PHP type Ia and their family members with pseudoPHP have an approximately 50% reduction in $G\alpha_s$ activity, as determined by functional assays of membranes from a variety of freshly obtained tissues and cultured cells, including red blood cells (94) and cultured fibroblasts (123). In

TABLE 3. Clinical and molecular characteristics of patients with Albright hereditary osteodystrophy (AHO) and pseudohypoparathyroidism (PHP)*

	Molecular Defect	Inheritance	AHO	Hormone Resistance	Response to PTH
AHO phenocopy	del 2q37	Sporadic	Yes	No	Normal
PseudoPHP	Various mutations in $G\alpha_s$	AD ? imprinting	Yes	No	Normal
PHP Ia				Multiple	Blunted ↑cAMP Blunted ↑TRP
PHP Ib	No mutations in PTH/PTHrP receptor	AD	No	PTH only	
PHP Ic	? adenylyl cyclase	AD	Yes	Multiple	
PHP II	? vitamin D status	Sporadic	No	PTH only	Blunted ↑TRP

Abbreviations: AD = autosomal dominant; PTH = parathyroid hormone; cAMP = cyclic AMP; PTHrP = PTH-related protein.

* Patients with the AHO phenotype may have identical $G\alpha_s$ mutations associated with (PHP Ia) or without (pseudoPHP) hormone resistance in the same family, but not in the same generation. Each family has a unique mutation (see Table 4 and Figure 3). Less commonly, patients may have isolated resistance to PTH as defined by the absence of urinary cAMP and phosphaturic (TRP) responses to PTH infusion (PHP Ib and II); these patients do not have the AHO phenotype and the genetic defects are unknown. Rare patients with the AHO phenotype and hormone resistance but without a $G\alpha_s$ mutation have been described (PHP Ic). The molecular cause is unknown. The inheritance patterns are variable.

most cases, these functional deficiencies are correlated with decreased levels of $G\alpha_s$ mRNA, as measured by Northern blot analysis (91), and reduced $G\alpha_s$ protein, as measured by quantitative immunoblot analysis (123). However, in some cases levels of $G\alpha_s$ mRNA and $G\alpha_s$ protein are normal despite reduced $G\alpha_s$ bioactivity (91). Molecular analysis has revealed that a unique heterozygous *GNAS1* gene mutation accounts for $G\alpha_s$ deficiency in each kindred studied (Table 4, Figure 3). These various mutations include an initiator codon mutation (122), missense mutations (110, 165), mutations in sequences necessary for correct splicing (110), and small deletions (120, 164).

In patients with PHP type Ib hormone resistance is limited to PTH. Thus, it was hypothesized that PHP type Ib patients would have genetic defects in the PTH/PTHrP receptor. However, careful analyses of the PTH/PTHrP receptor gene (137) and mRNA (Ding and Levine, unpublished results) from PHP type Ib patients have failed to identify any mutations in the coding sequences. More recently, linkage analysis of a silent polymorphism in the PTH/PTHrP gene in several families with PHP type Ib has shown that the PTH/PTHrP receptor is not linked to inheritance of PHP type Ib (Ding and Levine, unpublished results). Although it is generally accepted that the PTH/PTHrP receptor is the physiologically important receptor for PTH action, a second gene encoding a PTH receptor with different signaling properties has recently been identified (157).

Inheritance of AHO and hormone resistance

Early clinical studies of AHO demonstrated a female:male ratio of 2:1 among affected individuals, which led to the suggestion that AHO is an X-linked disorder. However, the description of a family in which male to male transmission occurred (159), and the subsequent localization of the human *GNAS1* gene to chromosome 20 (95) have led to the conclusion that AHO is inherited in an autosomal dominant fashion with sex modification (159) (see Table 3).

Patients with PHP type Ia and patients with pseudoPHP are frequently present in a single family, but PHP type Ia and psuedoPHP do not occur in the same generation. This observation has argued against random, as well as some nonrandom (for example, metabolic interference [70]), mechanisms as the basis for the AHO phenotypes. Moreover, in most families inheritance of $G\alpha_s$ deficiency from the father leads to pseudoPHP whereas inheritance from the mother leads to PHP type Ia. This pattern of inheritance has suggested that genomic imprinting may be involved in determining whether patients with AHO have hormone resistance (that is, PHP type Ia) or hormone responsiveness (that is, pseudoPHP) (38). However, several lines of evidence now argue against this theory: 1) in 1 reported family (140) inheritance of $G\alpha_s$ deficiency from either a father or mother led to hormone resistance (that is, PHP type Ia) in the affected children; 2) both $G\alpha_s$ alleles are expressed in a variety of human fetal tis-

TABLE 4. Mutations of *GNAS1* described in patients with Albright hereditary osteodystrophy*

Mutation	$G\alpha_s$ mRNA	$G\alpha_s$ Protein	$G\alpha_s$ Bioactivity	Comments (Reference)
$Met^{1}\rightarrow Val$	~100%	↓, abnl	~50%	(122)
A→G				Acceptor splice: intron 3, unpublished
43-bpdeletion	ND	ND	81%	Exon 4 (120)
$Leu^{99}\rightarrow Pro$	ND	~50%	ND	(110)
$Arg^{165}\rightarrow Cys$	~100%	~50%	ND	(110)
$Tyr^{190}\rightarrow Asp$				Unpublished
4-bp deletion	~50%	ND	ND	Exon 7 (164)
4-bp deletion	~100%	~50%	ND	Exon 8 (110)
G→C	↓	ND	ND	Donor splice: intron 10 (165)
1-bp deletion	ND	ND	ND	Exon 10 (165)
$Ala^{366}\rightarrow Ser$	ND	nl 33° ↓ 37°	↑ 33° ↓ 37°	Testotoxicosis (67)
ΔIle^{383}				Unpublished
$Arg^{385}\rightarrow His$	ND	~100%	41%	Uncoupled (142)

Abbreviations: abnl = abnormal; ND = not determined; nl = normal.

* A unique *GNAS1* mutation has been identified in each family with members affected with Albright hereditary osteodystrophy. The relative amounts of $G\alpha_s$ gene transcribed into mRNA and translated into protein as well as the bioactivity of the mutant protein products are variable. Figure 3 displays the *GNAS1* mutations and the positions of the mutation in the protein.

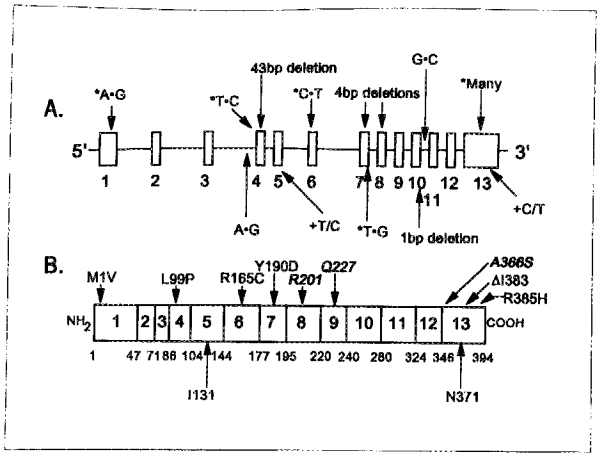

FIG. 3. Mutations in the *GNAS1* gene. Panel **A** depicts the human *GNAS1* gene, which contains at least 13 exons and 12 introns and spans over 20-kilobase pairs. Thirteen unique mutations that result in loss of $G\alpha_s$ function have been identified in 13 unrelated Albright hereditary osteodystrophy (AHO) families; missense mutations are denoted by the symbol *. Panel **B** depicts the position of these mutations above the protein structure. Two polymorphisms are denoted by the symbol + in panel **A**, and the position of the unchanged amino acid is denoted beneath the predicted $G\alpha_s$ protein in panel **B**. The sites of 2 missense mutations that result in gain of function found in McCune-Albright syndrome and in some sporadic endocrine tumors are depicted in italics in panel **B**. The effects of the mutations in AHO patients are summarized in Table 4 and in the text.

sues (18), cultured fibroblasts (110), and ovarian tissue (Namnoun and Levine, unpublished); 3) in all tissues/cells that have been examined, levels of $G\alpha_s$ protein and activity are similarly reduced in patients with or without hormone resistance (123).

An AHO-like phenotype has also been described in several individuals in association with a deletion in chromosome 2q37.2 (124, 170). These patients have brachydactyly and short stature but lack evidence of heterotopic ossification. Immunoreactive $G\alpha_s$ is normal and there is no evidence of hormone resistance (124). This newly described syndrome may represent a phenocopy of the developmental defects that occur in patients with AHO due to $G\alpha_s$ deficiency. Identification of the gene(s) missing in these individuals may lend insight into the pathophysiologic basis for AHO in PHP type Ia.

Clinical variability of AHO

Subjects with $G\alpha_s$ deficiency manifest considerable variability in the clinical presentation of AHO, even in affected members of the same family. Whereas patients with pseudoPHP typically have normal intelligence, patients with PHP type Ia show a spectrum of cognitive function ranging from normal to profoundly impaired. Obesity and skeletal dysplasias such as round facies, short stature, and brachydactyly may be obvious in some subjects and subtle (or even absent) in others. Subcutaneous ossifications are present in approximately one-half of patients with $G\alpha_s$ deficiency, and are unrelated to hypocalcemia or hyperphosphatemia.

There does not appear to be a correlation between the expression of AHO and the extent of hormone resistance, suggesting a direct effect of $G\alpha_s$ deficiency on skeletal development. Recent studies of the receptor for PTH provide some insights into the nature of this effect. There is a single receptor for both PTH and PTH-related protein (2). Transgenic mice in which both alleles of the gene encoding PTHrP are disrupted develop severe skeletal dysplasias that are fatal in the neonatal period (74). Thus the role of $G\alpha_s$ in development of AHO may be more related to skeletal resistance to PTHrP than to PTH.

Patients with PHP type Ia manifest target organ resistance not only to PTH but also to additional hormones that activate adenylyl cyclase. Most patients have subclinical hypothyroidism with a low or low normal serum concentrations of thyroxine. Basal levels of serum TSH are generally elevated and show an exaggerated response to TRH. The thyroid gland is not enlarged despite elevated serum concentrations of TSH. Clinically significant hypothyroidism occurs in some patients, and may provide the initial clue to a diagnosis of PHP type Ia (93). Women with PHP type Ia frequently have abnormal ovarian function and in some cases have elevated serum levels of gonadotropins and show exaggerated LH and FSH responses to administered GnRH. Remarkably, patients with PHP type Ia do not show abnormal responses to all hormones that stimulate adenylyl cyclase. For example, PHP type Ia patients have normal physiologic responses to ACTH, vasopressin, and glucagon, suggesting (at least in the case of the hepatic response to glucagon) that in some tissues submaximal increases in intracellular cAMP are adequate to generate a physiologic hormone response (112).

Several features of the variability in hormone resistance in different target tissues remain to be explained: 1) hormone resistance does not occur in all tissues in which receptor activation leads to stimulation of adenylyl cyclase; 2) hormone resistance does not occur in the same target tissues in all patients; and 3) not all patients with AHO and deficiency of $G\alpha_s$ have hormone resistance (pseudoPHP).

Summary

Inactivating and activating mutations in the gene encoding $G\alpha_s$ (GNAS1) are known to be the basis for 2 well-described contrasting clinical disorders,

Albright hereditary osteodystrophy (AHO) and McCune-Albright syndrome (MAS). AHO is an autosomal dominant disorder due to germline mutations in GNAS1 that decrease expression or function of $G\alpha_s$ protein. Loss of $G\alpha_s$ function leads to tissue resistance to multiple hormones whose receptors couple to $G\alpha_s$. By contrast, MAS results from postzygotic somatic mutations in GNAS1 that lead to enhanced function of $G\alpha_s$ protein. Acquisition of the activating mutation early in life leads to a more generalized distribution of the mosaicism and is associated with the classic clinical triad of polyostotic fibrous dysplasia, endocrine hyperfunction, and café au lait skin lesions described in MAS. Acquisition of a similar activating mutation in GNAS1 later in life presumably accounts for the restricted distribution of the gsp oncogene, and is associated with the development of isolated lesions (for example, fibrous dysplasia, pituitary or thyroid tumors) without other manifestations of MAS. Tissues that are affected by loss of $G\alpha_s$ function in AHO are also affected by gain of $G\alpha_s$ function in MAS, thus identifying specific tissues in which the second messenger cAMP plays a dominant role in cell growth, proliferation, or function. Further investigations of the functions of $G\alpha_s$ and other members of the GTPase binding protein family will provide more insight into the pathogenesis and clinical manifestations of human disease.

References

1. Aarskog D, Tverteraas E. McCune-Albright's syndrome following adrenalectomy for Cushing's syndrome in infancy. J Pediatr 73: 89–96, 1968.
2. Abou-Samra AB, Jüppner H, Force T, Freeman MW, Kong XF, Schipani E, Urena P, Richards J, Bonventre JV, Potts JT Jr, Kronenberg HM, Segre GV. Expression cloning of a common receptor for parathyroid hormone and parathyroid hormone-related peptide from rat osteoblast-like cells: A single receptor stimulates intracellular accumulation of both cAMP and inositol trisphosphates and increases intracellular free calcium. Proc Natl Acad Sci U S A 89: 2732–36, 1992.
3. Abs R, Beckers A, Van de Vyver FL, De Schepper A, Stevenaert A, Hennen G. Acromegaly, multinodular goiter, and silent polyostotic dysplasia. A variant of the McCune-Albright syndrome. J Endocrinol Invest 13: 671–75, 1990.
4. Albin J, Wu R. Abnormal hypothalamic-pituitary function in polyostotic fibrous dysplasia. Clin Endocrinol 14: 435–43, 1981.
5. Albright F, Burnett CH, Smith PH. Pseudo-hypoparathyroidism: An example of "Seabright-Bantam syndrome." Endocrinology 30: 922–32, 1942.
6. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and endocrine dysfunction, with precocious puberty in females. N Engl J Med 216: 727–41, 1937.
7. Albright F, Forbes AP, Henneman PH. Pseudo-pseudohypoparathyroidism. Trans Assoc Am Physicians 65: 337–50, 1952.
8. Allgeier A, Offermanns S, Van Sande J, Spicher K, Schultz G, Dumont JE. The human thyrotropin receptor activates G-proteins Gs and Gq/11. J Biol Chem 269: 13733–35, 1994.
9. Benjamin D, McRoberts J. Polyostotic fibrous dysplasia associated with Cushing syndrome: Case report with autopsy findings. Arch Pathol 96: 175–78, 1973.
10. Benovic JL, DeBlasi A, Stone WC, Caron MG, Lefkowitz RJ. Beta-adrenergic receptor kinase: Primary structure delineates a multigene family. Science 246: 235–40, 1989.
11. Berlot CH, Bourne HR. Identification of effector-activating residues of Gsa. Cell 68: 911–22, 1992.
12. Birnbaumer L, Abramowitz J, Yatani A, Okabe K, Mattera R, Sanford J, Codina J, Brown AM. Roles of G proteins in coupling of receptors to ionic channels and other effector systems. Crit Rev Biochem Molec Bio 24: 225–44, 1990.
13. Boepple PA, Frisch LS, Wierman ME, Hoffman WH, Crowley WF. The natural history of autonomous gonadal function, adrenarche, and central puberty in gonadotropin-independent precocious puberty. J Clin Endocrinol Metab 75: 1550–55, 1992.
14. Boothroyd CV, Grimmond SM, Cameron DP, Hayward NK. G protein mutations in tumours of the pituitary, parathyroid and endocrine pancreas. Biochem Biophys Res Commun 211: 1063–70, 1995.
15. Boston BA, Mandel S, LaFranchi S, Bliziotes M. Activating mutation in the stimulatory guanine nucleotide-binding protein in an infant with Cushing's syndrome and nodular adrenal hyperplasia. J Clin Endocrinol Metab 79: 890–93, 1994.
16. Bourne HR, Sanders DA, McCormick F. The GTPase superfamily: Conserved structure and molecular mechanism. Nature 349: 117–27, 1991.
17. Bray P, Carter A, Simons C, Guo V, Puckett C, Kamholz J, Spiegel A, Nirenberg M. Human cDNA clones for four species of Gsa signal transduction protein. Proc Natl Acad Sci U S A 83: 8893–97, 1986.
18. Campbell R, Gosden CM, Bonthron DT. Parental origin of transcription from the human GNAS1 gene. J Med Genet 31: 607–14, 1994.
19. Carr D, Mathie IK, Manners AR. Hyperprolactinemia in a patient with the McCune-Albright syndrome. Br J Obstet Gynecol 86: 330–31, 1979.
20. Cavanah SF, Dons RF. McCune-Albright syndrome: How many endocrinopathies can one patient have? South Med J 86: 364–67, 1993.
21. Cerione RA, Sibley DR, Codina J, Benovic JL, Winslow J, Neer EJ, Birnbaumer L, Caron MG, Lefkowitz RJ. Reconstitution of a hormone-sensitive adenylate cyclase system. The pure beta-adrenergic receptor and guanine nucleotide regulatory protein confer hormone responsiveness on the resolved catalytic unit. J Biol Chem 259: 9979–82, 1984.
22. Cerione RA, Staniszewski C, Benovic JL, Lefkowitz RJ, Caron MG, Gierschik P, Somers R, Spiegel AM, Codina J, Birnbaumer L. Specificity of the functional interactions of the beta-adrenergic receptor and rhodopsin with guanine nucleotide regulatory proteins reconstituted in phospholipid vesicles. J Biol Chem 260: 1493–1500, 1985.
23. Chanson P, Dib A, Visot A, Derome PJ. McCune-Albright syndrome and acromegaly: Clinical studies and responses to treatment in five cases. Eur J Endocrinol 131: 229–34, 1994.
24. Chase LR, Aurbach GD. Parathyroid function and the renal excretion of 3′5′-adenylic acid. Proc Natl Acad Sci U S A 58: 518–25, 1967.
25. Chase LR, Aurbach GD. The effect of parathyroid hormone on the concentration of adenosine 3′,5′-monophosphate in skeletal tissue in vitro. J Biol Chem 245: 1520–26, 1970.
26. Chase LR, Melson GL, Aurbach GD. Pseudohypoparathyroidism: Defective excretion of 3′,5′-AMP in response to parathyroid hormone. J Clin Invest 48: 1832–44, 1969.
27. Chen J, Iyengar R. Suppression of ras-induced transformation of NIH 3T3 cells by activated Gαs. Science 263: 1278–81, 1994.
28. Chung KF, Alaghband-Zadeh J, Guz A. Acromegaly and hyperprolactinemia in McCune-Albright syndrome. Am J Dis Child 137: 134–36, 1983.
29. Civitelli R, Reid IR, Westbrook S, Avioli LV, Hruska KA. PTH elevates inositol polyphosphates and diacylglycerol in a rat osteoblast-like cell line. Am J Physiol 255: E660-E667, 1988.
30. Clapham DE, Neer EJ. New roles for G-protein βγ-dimers in transmembrane signalling. Nature 365: 403–6, 1993.
31. Clementi E, Malgaretti N, Meldolesi J, Taramelli R. A new constitutively activating mutation of the Gs protein α subunit-gsp oncogene is found in human pituitary tumours. Oncogene 5: 1059–61, 1990.
32. Coleman DE, Berghuis AM, Lee E, Linder ME, Gilman AG, Sprang SR. Structures of active conformations of Gia1 and the mechanism of GTP hydrolysis. Science 265: 1405–12, 1994.
33. Cremonini N, Graziano E, Chiarini V, Sforza A, Zampa GA. Atypical McCune-Albright syndrome associated with growth hormone-prolactin pituitary adenoma: Natural history, long-term follow-up, and SMS 201–995-bromocriptine combined treatment results. J Clin Endocrinol Metab 75: 1166–69, 1991.
34. Crespo P, Xu N, Simonds WF, Gutkind JS. Ras-dependent activation of MAP kinase pathway mediated by G-protein βγ subunits. Nature 369: 418–20, 1994.
35. Cuttler L, Jackson JA, uz Zafar MS, Levitsky L, Mellinger RC, Frohman LA. Hypersecretion of growth hormone and prolactin in McCune-Albright syndrome. J Clin Endocrinol Metab 68: 1148–54, 1989.
36. D'Armiento M, Reda G, Camagna A, Tardella L. McCune-Albright syndrome: Evidence for autonomous multiendocrine hyperfunction. J Pediatr 102: 584–86, 1983.

37. Danon M, Robboy S, Kim S, Scully R, Crawford J. Cushing syndrome, sexual precocity, and polycystic fibrous dysplasia (Albright syndrome) in infancy. J Pediatr 87: 917–21, 1975.
38. Davies SJ, Hughes HE. Imprinting in Albright's hereditary osteodystrophy. J Med Genet 30: 101–3, 1993.
39. Dhanasekaran N, Heasley LE, Johnson GL. G protein coupled receptor systems involved in cell growth and oncogenesis. Endocr Rev 16: 259–70, 1995.
40. Dunlay R, Hruska K. PTH receptor coupling to phospholipase C is an alternate pathway of signal transduction in bone and kidney. Am J Physiol 258: F223-F231, 1990.
41. Econs MJ, Drezner MK. Tumor-induced osteomalacia—unveiling a new hormone. N Engl J Med 330: 1679–81, 1994.
42. Ehrig U, Wilson D. Fibrous dysplasia of bone and primary hyperparathyroidism. Ann Intern Med 77: 234–38, 1972.
43. Endo M, Yamada Y, Matsuura N, Niikawa N. Monozygotic twins discordant for the major signs of McCune-Albright syndrome. Am J Med Genet 41: 216–20, 1991.
44. Falconer MA, Cope CL, Robb-Smith AHT. Fibrous dysplasia of bone with endocrine disorders and cutaneous pigmentation (Albright's disease). Q J Med 11: 121–56, 1942.
45. Feuillan PP, Foster CM, Pescovitz OH, Hench KD, Shawker RT, Dwyer A, Malley JD, Barnes K, Loriaux DL, Cutler GB. Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testalactone. N Engl J Med 315: 1115–19, 1986.
46. Feuillan PP, Jones J, Cutler GB. Long term testalactone therapy for precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab 77: 647–51, 1993.
47. Feuillan PP, Jones J, Ross JL. Growth hormone hypersecretion in a girl with McCune-Albright syndrome: Comparison with controls and response to a dose of long-acting somatostatin analog. J Clin Endocrinol Metab 80: 1357–60, 1995.
48. Feuillan PP, Shawker T, Rose SR, Jones J, Jeevanram RK, Nisula BC. Thyroid abnormalities in the McCune-Albright syndrome: Ultrasonography and hormonal studies. J Clin Endocrinol Metab 71: 1596–1601, 1990.
49. Foster CM, Ross JL, Shawker T, Pescovitz OH, Loriaux DL, Cutler GB, Comite F. Absence of pubertal gonadotropin secretion in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 58: 1161–65, 1984.
50. Frisch LS, Copeland KC, Boepple PA. Recurrent ovarian cysts in childhood: Diagnosis of McCune-Albright syndrome by bone scan. Pediatr 90: 102–4, 1992.
51. Fukada Y, Ohguro H, Saito T, Yoshizawa T, Akino T. βγ-subunit of bovine transducin composed of two components with distinctive γ-subunits. J Biol Chem 264: 5937–43, 1989.
52. Geffner ME, Nagel RA, Dietrich RB, Kaplan SA. Treatment of acromegaly with a somatostatin analog in a patient with McCune-Albright syndrome. J Pediatr 111: 740–43, 1987.
53. Gilman AG. G proteins and dual control of adenylate cyclase. Cell 36: 577–79, 1984.
54. Gilman AG. Guanine nucleotide-binding regulatory proteins and dual control of adenylate cyclase. J Clin Invest 73: 1–4, 1984.
55. Goretzki PE, Lyons J, Stacy-Phipps S, Rosenau W, Demeure M, Clark OH, McCormick F, Roher H-D, Bourne HR. Mutational activation of ras and gsp oncogenes in differentiated thyroid cancer and their biological implications. World J Surg 16: 576–82, 1992.
56. Goretzki PE, Simon D, Roher H-D. G-protein mutations in thyroid tumors. Exp Clin Endocrinol 100: 14–16, 1992.
57. Graziano MP, Gilman AG. Synthesis in *Escherichia coli* of GTPase-deficient mutants of Gsa. J Biol Chem 264: 15475–82, 1989.
58. Guo J, Iida-Klein A, Huang X, Abou-Samra AB, Segre GV, Bringhurst FR. Parathyroid hormone (PTH)/PTH-related peptide receptor density modulates activation of phospholipase C and phosphate transport by PTH in LLC-PK1 cells. Endocrinology 136: 3884–91, 1995.
59. Hahn SB, Lee SB, Kim DH. Albright's syndrome with hypophosphatemic rickets and hyperthyroidism—a case report. Yonsei Med J 32: 179–83, 1991.
60. Happle R. The McCune-Albright syndrome: A lethal gene surviving by mosaicism. Clin Genet 29: 321–24, 1986.
61. Harris RI. Polyostotic fibrous dysplasia with acromegaly. Am J Med 78: 539–42, 1985.
62. Harris WH, Dudley HR, Barry RJ. The natural history of fibrous dysplasia. J Bone Joint Surg 44-A: 207–33, 1962.
63. Hauffa BP, Havers W, Stolecke H. Short-term effects of testalactone compared to other treatment modalities on longitudinal growth and ovarian activity in a girl with McCune-Albright syndrome. Helv Paediatr Acta 42: 471–80, 1987.
64. Hausdorff WP, Hnatowich M, O'Dowd BF, Caron MG, Lefkowitz RJ. A mutation of the beta 2-adrenergic receptor impairs agonist activation of adenylyl cyclase without affecting high affinity agonist binding. Distinct molecular determinants of the receptor are involved in physical coupling to and functional activation of Gs. J Biol Chem 265: 1388–93, 1990.
65. Hellevuo K, Yoshimura M, Kao M, Hoffman PL, Cooper DMF, Tabakoff B. A novel adenylyl cyclase sequence cloned from the human erythroleukemia cell line. Biochem Biophys Res Commun 192: 311–18, 1993.
66. Huang TS, Chang CC, Huang JS, Hsieh HC, Chen FW. Albright's syndrome with acromegaly and Hashimoto's thyroiditis: Report of a case. J Formos Med Assoc 89: 714–18, 1990.
67. Iiri T, Herzmark P, Nakamoto JM, Dop CV, Bourne HR. Rapid GDP release from Gsα in patients with gain and loss of endocrine function. Nature 371: 164–68, 1994.
68. Inamo Y, Hanawa Y, Kin H, Okuni M. Findings on magnetic resonance imaging of the spine and femur in a case of McCune-Albright syndrome. Pediatr Radiol 23: 15–18, 1993.
69. Ishikawa Y, Bianchi C, Nadal-Ginard B, Homcy CJ. Alternative promoter and 5′ exon generate a novel $G_s\alpha$ mRNA. J Biol Chem 265: 8458–62, 1990.
70. Johnson WG. Metabolic interference and the +- heterozygote. A hypothetical form of simple inheritance which is neither dominant nor recessive. Am J Hum Genet 32: 374–86, 1980.
71. Joishy SK, Morrow LB. McCune-Albright syndrome associated with a functioning pituitary chromophobe adenoma. J Pediatr 89: 73–75, 1976.
72. Journot L, Pantaloni C, Bockaert J, Audigier Y. Deletion within the amino-terminal region of Gsa impairs its ability to interact with βγ subunits and to activate adenylate cyclase. J Biol Chem 266: 9009–15, 1991.
73. Kahn RA, Gilman AG. ADP-ribosylation of Gs promotes the dissociation of its α and β subunits. J Biol Chem 259: 6235–40, 1984.
74. Karaplis AC, Luz A, Glowacki J, Bronson RT, Tybulewicz VLJ, Kronenberg HM, Mulligan RC. Lethal skeletal dysplasia from targeted disruption of the parathyroid hormone-related peptide gene. Genes Dev 8: 277–89, 1994.
75. Katada T, Bokoch GM, Northup JK, Ui M, Gilman AG. The inhibitory guanine nucleotide-binding regulatory component of adenylate cyclase. Properties and function of the purified protein. J Biol Chem 259: 3568–77, 1984.
76. Kehlenbach RH, Matthey J, Huttner WB. XLas is a new type of G protein. Nature 372: 804–8, 1994.
77. Kessel D, Hall CM, Shaw DG. Two unusual cases of nephrocalcinosis in infancy. Pediatr Radiol 22: 470–71, 1992.
78. Kim D, Lewis DL, Graziadei L, Neer EJ, Bar-Sagi D, Clapham DE. G-protein βγ-subunits activate the cardiac muscarinic potassium channel via phospholipase A2. Nature 337: 557, 1989.
79. Kleuss C, Scherubl H, Hescheler J, Schultz G, Wittig B. Different β-subunits determine G-protein interactions with transmembrane receptors. Nature 358: 424–26, 1992.
80. Kovacs K, Horvath E, Thorner MO, Rogol AD. Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with the McCune-Albright syndrome. Virchows Archiv (Pathol Anat) 403: 77–86, 1984.
81. Kozasa T, Itoh H, Tsukamoto T, Kaziro Y. Isolation and characterization of the human Gsa gene. Proc Natl Acad Sci U S A 85: 2081–85, 1988.
82. Kumawat DC, Bomb BS, Agarwal HK, Bhatnagar HNS. The Albright syndrome associated with acromegaly and hyperthryoidism (a case report). J Postgrad Med 33: 155–57, 1987.
83. Kupcha PC, Guille JT, Tassanawipas A, Bowen JR. Polyostotic fibrous dysplasia and acromegaly. J Pediatr Orthop 11: 95–99, 1991.
84. Lambright DG, Noel JP, Hamm HE, Sigler PB. Structural determinants for activation of the α-subunit of a heterotrimeric G protein. Nature 369: 621–28, 1994.
85. Landis CA, Harsh G, Lyons J, Davis RL, McCormick F, Bourne HR. Clinical characteristics of acromegalic patients whose pituitary tumors contain mutant Gs protein. J Clin Endocrinol Metab 71: 1416–20, 1990.
86. Landis CA, Masters SB, Spada A, Pace AM, Bourne HR, Vallar L. GTPase inhibiting mutations activate the α chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. Nature 340: 692–96, 1989.
87. Ledent C, Dumont JE, Vassart G, Parmentier M. Thyroid expression of an A2 adenosine receptor transgene induces thyroid hyperplasia and hyperthyroidism. EMBO J 11: 537–42, 1992.
88. Lee PA, Van Dop C, Migeon CJ. McCune-Albright syndrome. Long term follow-up. JAMA 256: 2980–84, 1986.

89. Lester PD, McAlister WH. Fibrous dysplasia and precocious puberty (McCune-Albright syndrome). South Med J 72: 631–32, 1979.
90. Lever EG, Pettingale KW. Albright's syndrome associated with a soft-tissue myxoma and hypophosphatemic osteomalacia. J Bone Joint Surg 65B: 621–26, 1983.
91. Levine MA, Ahn TG, Klupt SF, Kaufman KD, Smallwood PM, Bourne HR, Sullivan KA, Van Dop C. Genetic deficiency of the α subunit of the guanine nucleotide-binding protein Gs as the molecular basis for Albright hereditary osteodystrophy. Proc Natl Acad Sci U S A 85: 617–21, 1988.
92. Levine MA, Downs RW Jr, Moses AM, Breslau NA, Marx SJ, Lasker RD, Rizzoli RE, Aurbach GD, Spiegel AM. Resistance to multiple hormones in patients with pseudohypoparathyroidism. Association with deficient activity of guanine nucleotide regulatory protein. Am J Med 74: 545–56, 1983.
93. Levine MA, Jap TS, Hung W. Infantile hypothyroidism in two sibs: An unusual presentation of pseudohypoparathyroidism type Ia. J Pediatr 107: 919–22, 1985.
94. Levine MA, Jap TS, Mauseth RS, Downs RW, Spiegel AM. Activity of the stimulatory guanine nucleotide-binding protein is reduced in erythrocytes from patients with pseudohypoparathyroidism and pseudopseudohypoparathyroidism: Biochemical, endocrine, and genetic analysis of Albright's hereditary osteodystrophy in six kindreds. J Clin Endocrinol Metab 62: 497–502, 1986.
95. Levine MA, Modi WS, O'Brien SJ. Mapping of the gene encoding the α subunit of the stimulatory G protein of adenylyl cyclase (GNAS1) to 20q13.2→q13.3 in human by in situ hybridization. Genomics 11: 478–79, 1991.
96. Levine MA, Smallwood PM, Moen PT Jr, Helman LJ, Ahn TG. Molecular cloning of β3 subunit, a third form of the G protein β-subunit polypeptide. Proc Natl Acad Sci U S A 87: 2329–33, 1990.
97. Levitzki A, Rudick J, Pastan I, Vass WC, Lowy DR. Adenylate cyclase activity of NIH 3T3 cells morphologically transformed by ras genes. FEBS Lett 197: 134–38, 1986.
98. Lightner ES, Penny R, Frasier SD. Growth hormone excess and sexual precocity in polyostotic fibrous dysplasia (McCune-Albright syndrome): Evidence for abnormal hypothalamic function. J Pediatr 87: 922–27, 1975.
99. Lipson A, Hsu T-H. The Albright syndrome associated with acromegaly: Report of a case and review of the literature. Johns Hopkins Med J 149: 10–14, 1981.
100. Lyons J, Landis CA, Griffith H, Vallar L, Grunewald K, Feichtinger H, Duh QY, Clark OH, Kawasaki E, Bourne HR, McCormick F. Two G protein oncogenes in human endocrine tumors. Science 249: 655–59, 1990.
101. Majzoub JA, Scully RE. A six-year-old boy with multiple bone lesions, repeated fractures, and sexual precocity. N Engl J Med 328: 496–502, 1993.
102. Malchoff CD, Reardon G, MacGillivray DC, Yamase H, Rogol AD, Malchoff DM. An unusual presentation of McCune-Albright syndrome confirmed by an activating mutation of the Gsa-subunit from a bone lesion. J Clin Endocrinol Metab 78: 803–6, 1994.
103. Manna C, Epifano O, Riminucci M, Baschieri L, Stefanini M, Canipari R. In vitro production of estradiol by ovarian granulosa cells in a case of McCune-Albright syndrome. J Endocrinol Invest 14: 311–15, 1991.
104. Masters SB, Sullivan KA, Miller RT, Beiderman B, Lopez NG, Ramachandran J, Bourne HR. Carboxyl terminal domain of Gsa specifies coupling of receptors to stimulation of adenylyl cyclase. Science 241: 448–51, 1988.
105. Matsuo K, Friedman E, Gejman P, Fagin J. The thyrotropin receptor (TSH-R) is not an oncogene for thyroid tumors: Structural studies of the TSH-R and the α-subunit of Gs in human thyroid neoplasms. J Clin Endocrinol Metab 76: 1446–51, 1993.
106. Mauras N, Blizzard RM. The McCune Albright syndrome. Acta Endocrinol 256 Suppl: 207–17, 1986.
107. McCune DJ, Bruch H. Osteodystrophia fibrosa. Am J Dis Child 54: 806–48, 1937.
108. Meinkoth JL, Goldsmith PK, Spiegel AM, Feramisco JR, Burrow GN. Inhibition of thyrotropin-induced DNA synthesis in thyroid follicular cells by microinjection of an antibody to the stimulatory G protein of adenylate cyclase, Gs. J Biol Chem 267: 13239–45, 1992.
109. Michiels F, Caillou B, Talbot M, Dessarps-Freichey F, Maunoury M-T, Schlumberger M, Mercken L, Monier R, Feunteun J. Oncogenic potential of guanine nucleotide stimulatory factor α subunit in thyroid glands of transgenic mice. Proc Natl Acad Sci U S A 91: 10488–92, 1994.
110. Miric A, Vechio JD, Levine MA. Heterogeneous mutations in the gene encoding the α-subunit of the stimulatory G protein of adenylyl cyclase in Albright hereditary osteodystrophy. J Clin Endocrinol Metab 76: 1560–68, 1993.
111. Misaki M, Shima T, Ikoma J, Morioka K, Suzuki S. Acromegaly and hyperthryoidism associated with McCune-Albright syndrome. Horm Res 30: 26–27, 1988.
112. Moses AM, Weinstock RS, Levine MA, Breslau NA. Evidence for normal antidiuretic responses to endogenous and exogenous arginine vasopressin in patients with guanine nucleotide-binding stimulatory protein-deficient pseudohypoparathyroidism. J Clin Endocrinol Metab 62: 221–24, 1986.
113. Nakamoto JM, Jones EA, Zimmerman D, Scott ML, Donlan MA, Van Dop C. A missense mutation in the Gsa gene is associated with pseudohypoparathyroidism type I-A (PHP I-A) and gonadotropin-independant precocious puberty (GIPP). Clin Res 41: 40A, 1993.
114. Nemoz G, Sette C, Hess M, Muca C, Vallar L, Conti M. Activation of cyclic nucleotide phosphodiesterases in FRTL-5 thyroid cells expressing a constitutively active Gs alpha. Mol Endocrinol 9: 1279–87, 1995.
115. Noel JP, Hamm HE, Sigler PB. The 2.2 A cyrstal structure of transducin-a complexed with GTPgS. Nature 366: 654–63, 1993.
116. Nomura N, Miyajima N, Sazuka T, Tanaka A, Kawarabayasi Y, Sato S, Nagase T, Seki N, Ishikawa K, Tabata S. Prediction of the coding sequences of unidentified human genes. I. The coding sequences of 40 new genes (KIAA0001-KIAA0040) deduced by analysis of randomly sampled cDNA clones from human immature myeloid cell line KG-1. DNA Res 1: 27–35, 1994.
117. O'Sullivan C, Barton CM, Staddon SL, Brown CL, Lemoine NR. Activating point mutations of the gsp oncogene in human thyroid adenomas. Mol Carcinogenesis 4: 345–49, 1991.
118. Osawa S, Dhanasekaran N, Woon CW, Johnson GL. Gαi-Gαs chimeras define the function of α chain domains in control of G protein activation and βγ subunit complex interactions. Cell 63: 697–706, 1990.
119. Ostrowski J, Kjelsberg MA, Caron MG, Lefkowitz RJ. Mutagenesis of the beta 2-adrenergic receptor: How structure elucidates function. Annu Rev Pharmacol Toxicol 32: 167–83, 1992.
120. Oude Luttikhuis MEM, Wilson LC, Leonard JV, Trembath RC. Characterization of a de novo 43-bp deletion of the Gsα gene (GNAS1) in Albright hereditary osteodystrophy. Genomics 21: 455–57, 1994.
121. Pacini F, Perri G, Bagnolesi P, Cilotti A, Pinchera A. McCune-Albright syndrome with gigantism and hyperprolactinemia. J Endocrinol Invest 10: 417–20, 1987.
122. Patten JL, Johns DR, Valle D, Eil C, Gruppuso PA, Steele G, Smallwood PM, Levine MA. Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in Albright's hereditary osteodystrophy. N Engl J Med 322: 1412–19, 1990.
123. Patten JL, Levine MA. Immunochemical analysis of the α-subunit of the stimulatory G-protein of adenylyl cyclase in patients with Albright's hereditary osteodystrophy. J Clin Endocrinol Metab 71: 1208–14, 1990.
124. Phelan MC, Rogers C, Clarkson KB, Bowyer FP, Levine MA, Estabrooks LL, Severson MC, Dobyns WB. Albright hereditary osteodystrophy and del(2)(q37.3) in four unrelated individuals. Am J Med Genet 58: 1–7, 1995.
125. Pitcher J, Lohse MJ, Codina J, Caron MG, Lefkowitz RJ. Desensitization of the isolated beta 2-adrenergic receptor by beta-adrenergic receptor kinase, cAMP-dependent protein kinase, and protein kinase C occurs via distinct molecular mechanisms. Biochemistry 31: 3193–97, 1992.
126. Pitcher JA, Inglese J, Higgins JB, Arriza JL, Casey PJP, Kim C, Benovic JL, Kwatra MM, Caron MG, Lefkowitz RJ. Role of βγ subunits of G proteins in targeting the beta-adrenergic receptor kinase to membrane bound-receptors. Science 257: 1264–67, 1992.
127. Polychronakos C, Tsoukas G, Ducharme JR, Letarte J, Collu R. Gigantism and hyperprolactinemia in polyostotic fibrous dysplasia (McCune-Albright syndrome). J Endocrinol Invest 5: 323–26, 1982.
128. Powell DGB. Polyostotic fibrous dysplasia with acromegaly (Albright's syndrome): A case report. S Afr Med J 50: 182, 1976.
129. Prayson MA, Leeson MC. Soft-tissue myxomas and fibrous dysplasia of bone: A case report and review of the literature. Clin Orthop Rel Res 291: 222–28, 1993.
130. Premawardhana LDKE, Vora JP, Mills R, Scanlon MF. Acromegaly and its treatment in the McCune-Albright syndrome. Clin Endocrinol 36: 605–8, 1992.
131. Pronk GL, Bos JL. The role of p21 ras in receptor tyrosine kinase signalling. Biochim Biophys Acta 1198: 131–47, 1994.
132. Pun KK, Chan G, Kung A, Lam K, Chan FL, Wang C. McCune-Albright syndrome with acromegaly. Horm Metab Res 21: 527–28, 1989.
133. Rahmatullah M, Ginnan R, Robishaw JD. Specificity of G Protein α-γ subunit interactions. J Biol Chem 270: 2946–51, 1995.

134. Rahmatullah M, Robishaw JD. Direct interaction of the α and γ subunits of the G proteins. J Biol Chem 269: 3574–80, 1994.
135. Rhee SG, Chol KD. Regulation of inositol phospholipid-specific phospholipase C isozymes. J Biol Chem 267: 12393–96, 1992.
136. Ruggieri P, Sim FH, Bond JR, Unni KK. Malignancies in fibrous dysplasia. Cancer 73: 1411–24, 1994.
137. Schipani E, Weinstein LS, Bergwitz C, Iida-Klein A, Kong XF, Stuhrmann M, Kruse K, Whyte MP, Murray T, Schmidtke J, Van Dop C, Brickman AS, Crawford JD, Potts JT Jr, Kronenberg HM, Segre GV, Jüppner H. Pseudohypoparathyroidism type Ib is not caused by mutations in the coding exons of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene. J Clin Endocrinol Metab 80: 1611–21, 1995.
138. Schmidt CJ, Neer EJ. In vitro synthesis of G protein β γ dimers. J Biol Chem 266: 4538–44, 1991.
139. Schmidt CJ, Thomas TC, Levine MA, Neer EJ. Specificity of G protein β and γ subunit interactions. J Biol Chem 267: 13807–10, 1992.
140. Schuster V, Kress W, Kruse K. Paternal and maternal transmission of pseudohypoparathyroisism type Ia in a family with Albright hereditary osteodystrophy: No evidence of genomic imprinting [letter]. J Med Genet 31: 84, 1994.
141. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the α subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci U S A 89: 5152–56, 1992.
142. Schwindinger WF, Miric A, Zimmerman D, Levine MA. A novel $G_s\alpha$ mutant in a patient with Albright hereditary osteodystrophy uncouples cell surface receptors from adenylyl cyclase. J Biol Chem 269: 25387–91, 1994.
143. Scully RE, Mark EJ, McNeely WF, McNeely BU, eds. Case records of the Massachusetts General Hospital: Case 7–1993. N Engl J Med 328: 496–502, 1993.
144. Scurry MT, Bicknell JM, Fajans SS. Polyostotic fibrous dysplasia and acromegaly. Arch Intern Med 114: 40–45, 1964.
145. Shenker A, Sweet DE, Spiegel AM, Weinstein LS. An activating $G_s\alpha$ mutation is present in fibrous dysplasia of bone in the McCune-Albright syndrome. J Clin Endocrinol Metab 79: 750–75, 1994.
146. Shenker A, Weinstein LS, Moran A, Pescovitz OH, Charest NJ, Boney CM, Van Wyk JJ, Merino MJ, Feuillan PP, Spiegel AM. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of the stimulatory G protein Gs. J Pediatr 123: 509–18, 1993.
147. Sherman SI, Ladenson PW. Octreotide therapy of growth hormone excess in the McCune-Albright syndrome. J Endocrinol Invest 15: 185–90, 1992.
148. Shih TY, Hattori S, Clanton DJ, Ulsh LS, Chen ZQ, Lautenberger JA, Papas TS. Structure and function of p21 ras proteins. Gene Amplif Anal 4: 53–72, 1986.
149. Sibley DR, Lefkowitz RJ. Beta-adrenergic receptor-coupled adenylate cyclase. Biochemical mechanisms of regulation. Mol Neurobiol 1: 121–54, 1987.
150. Spada A, Arosio M, Bochicchio D, Bazzoni N, Vallar L, Bassetti M, Faglia G. Clinical, biochemical, and morphological correlates in patients bearing growth hormone-secreting pituitary tumors with or without constitutively active adenylyl cyclase. J Clin Endocrinol Metab 71: 1421–26, 1990.
151. Suarez HG, du Villard JA, Caillou B, Schlumberger M, Parmentier C, Monier R. Gsp mutations in human thyroid tumours. Oncogene 6: 677–79, 1991.
152. Swislocki AL, Camargo CA, Hoffman AR. McCune-Albright Syndrome: A case of primary hypogonadism obscured by hyperprolactinemic hypogonadotropic hypogonadism. West J Med 153: 653–56, 1990.
153. Tang WJ, Gilman AG. Type-specific regulation of adenylyl cyclase by G protein βγ subunits. Science 254: 1500–3, 1991.
154. Taussig R, Gilman AG. Mammalian membrane-bound adenylyl cyclases. J Biol Chem 270: 1–4, 1995.
155. Tordjman K, Stern N, Ouaknine G, Yossiphov Y, Razon N, Nordenskjold M, Friedman E. Activating mutations of the Gs alpha-gene in nonfunctioning pituitary tumors. J Clin Endocrinol Metab 77: 765–69, 1993.
156. Triantafillidou K, Antoniades K, Karakasis D, Rousso I, Drevelegas A. McCune-Albright syndrome: Report of a case. Oral Surg Oral Med Oral Pathol 75: 571–74, 1993.
157. Usdin TB, Gruber C, Bonner TI. Identification and functional expression of a receptor selectively recognizing parathyroid hormone, the PTH2 receptor. J Biol Chem 270: 15455–58, 1995.
158. Vallar L, Spada A, Giannattasio G. Altered Gs and adenylate cyclase activity in human GH-secreting pituitary adenomas. Nature 330: 566–68, 1987.
159. Van Dop C, Bourne HR, Neer RM. Father to son transmission of decreased Ns activity in pseudohypoparathyroidism type Ia. J Clin Endocrinol Metab 59: 825–28, 1984.
160. Van Sande J, Raspe E, Perret J, Lejeune C, Maenhaut C, Vassart G, Dumont JE. Thyrotropin activates both the cyclic AMP and the PIP2 cascades in CHO cells expressing the human cDNA of TSH receptor. Mol Cell Endocrinol 74: R1-R6, 1990.
161. Vessey SJ, Jones PM, Wallis SC, Schofield J, Bloom SR. Absence of mutations in the Gs alpha and Gi2 alpha genes in sporadic parathyroid adenomas and insulinomas. Clin Sci 87: 493–97, 1994.
162. Watson AJ, Katz A, Simon MI. A fifth member of the mammalian G-protein β-subunit family. J Biol Chem 269: 22150–56, 1994.
163. Wedegaertner PB, Wilson PT, Bourne HR. Lipid modifications of trimeric G proteins. J Biol Chem 270: 503–6, 1995.
164. Weinstein LS, Gejman PV, de Mazancourt P, American N, Spiegel AM. A heterozygous 4-bp deletion mutation in the Gsa gene (GNAS1) in a patient with Albright hereditary osteodystrophy. Genomics 13: 1319–21, 1992.
165. Weinstein LS, Gejman PV, Friedman E, Kadowaki T, Collins RM, Gershon ES, Spiegel AM. Mutations of the Gs α-subunit gene in Albright hereditary osteodystrophy detected by denaturing gradient gel electrophoresis. Proc Natl Acad Sci U S A 87: 8287–90, 1990.
166. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 325: 1688–95, 1991.
167. Williamson EA, Daniels M, Foster S, Kelly WF, Kendall-Taylor P, Harris PE. Gs alpha and Gi2 alpha mutations in clinically non-functioning pituitary tumors. Clin Endocrinol 41: 815–20, 1994.
168. Williamson EA, Ince PG, Harrison D, Kendall-Taylor P, Harris PE. G protein mutations in human pituitary adrenocorticotrophic hormone-secreting adenomas. Eur J Clin Invest 25: 128–31, 1995.
169. Williamson EA, Johnson SJ, Foster S, Kendall-Taylor P, Harris PE. G Protein mutations in patients with multiple endocrinopathies. J Clin Endocrinol Metab 80: 1702–5, 1995.
170. Wilson LC, Leverton K, Oude Luttikhuis ME, Oley CA, Flint J, Wolstenholme J. Brachydactyly and mental retardation: An Albright hereditary osteodystrophy-like syndrome localized to 2q37. Am J Hum Genet 56: 400–7, 1995.
171. Woon CW, Soparkar S, Heasley L, Johnson GL. Expression of a Gαs/Gαi chimera that constitutively activates cAMP synthesis. J Biol Chem 264: 5687–93, 1989.
172. Yoshimoto K, Iwahana H, Fukada A, Sano T, Itakura M. Rare mutations of the Gs α subunit gene in human endocrine tumors. Mutation detecteced by polymerase chain reaction-primer-introduced restriction analysis. Cancer 72: 1386–93, 1993.
173. Yoshimoto M, Nakayama M, Baba T, Uehara Y, Niikawa N, Ito M. A case of neonatal McCune-Albright syndrome with Cushing syndrome and hyperthyroidism. Acta Pediatr Scand 80: 984–87, 1991.
174. Zung A, Chalew SA, Schwindinger WF, Levine MA. Response to PTH(1–34) is altered in patients with McCune-Albright syndrome. J Bone Miner Res 8: S228, 1993.